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# PATENT SPECIFICATION

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## COMPLETE SPECIFICATION

### Pellets for Supplying Biologically Active Substances to Ruminants

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1. do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to pellets for supplying biologically active substances to ruminants, and to the manufacture thereof.

In British Patent specification No. 866,924, in the name of Commonwealth Scientific and Industrial Research Organisation, Australia, there are described and claimed pellets for administration to ruminants to supply them with biologically active substances for an extended period of time, said pellets having a density and weight which relatively permanently retains them in the rumeno-recticular sac of the animals after administration and lodgement in the sac and embodying a biologically active substance which is released from the pellets into the contents of the sac over the extended period of time. The biologically active substance is exemplified by trace elements, antilloat agents, antibiotics, anthelmintics, systemic insecticides and hormones.

The pellets are manufactured by embodying the active substance in a carrier binder or base, and also embodying if required a relatively dense material which makes the density and weight of the pellets above the minimum values below which an undesirably large proportion of the pellets tend to be ejected from the animals. The present invention provides an improvement in the composition and method of manufacture of these pellets.

The present invention, in one aspect, provides a pellet for administration to a ruminant to supply it with a biologically active substance for an extended period of time, said

pellet having a density and weight which relatively permanently retains it in the rumeno-recticular sac after administration and lodgement in the sac and embodying a core of density at least 3.5 around which there is an outer layer containing a biologically active substance which is released from the pellet into the contents of the sac over the extended period of time.

Preferably the material conferring the high density to the core is iron. The outer layer contains essentially one or more active substances, for example hormones, antilloat agents, antibiotics, anthelmintics, trace elements (such as cobalt, copper, manganese, molybdenum, iron, iodine, boron and vanadium) antihistamines and systemic insecticides which are capable of preventing attack by various external parasites. Both layers may contain other materials in various proportions depending on, for example, the amount and type of active substance required, the duration of biological action required, and the method of manufacture used. The core is not essentially situated centrally in the pellet.

The pellet may be manufactured by any one of several methods known to the art of pharmacy, whereby the core has applied around it the outer layer. The manufacture of the pellet by any of these methods is another aspect provided by the present invention.

The core may be formed by casting or by compression of granules of the core materials. Thus, the core may consist of iron in a fine powder which is granulated using a binding material, for example starch mucilage, gelatin solution or a solution of a "plastic" such as an acrylic resin in chloroform or cellulose acetate in acetone. The granules normally require a lubricating material, for example magnesium stearate, talc or graphite. A metallic oxide, for example cupric oxide, may be included in the granules when the oxide is to

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be heated; the oxide binds the granules together, so that a harder core is obtained.

The preferred method of manufacture of the pellet of the present invention is the compression coating technique, whereby the outer layer materials are compressed onto the core. This may be achieved using a compression coating machine in which outer layer materials, a pre-formed core and more outer layer materials are fed successively into each die cavity, so that each cavity contains a core surrounded by outer layer materials which are then compressed. In this method of manufacture, the core is preferably also formed by compression so that the core and pellet may be formed successively by the use of a compression coating machine in which one unit forms the core and a second unit coats it, or by the use of a compression coating machine in which one unit forms the core and the unit is then adjusted so that the outer layer is compressed onto the core. Thus, the core materials and the outer layer materials may be granulated separately; the core granules may then be compressed to form the core around which the outer layer granules are compressed.

The outer layer granules may contain a diluent, a binding material and a lubricating material. For example, when short periods of medication are required or when the proportion of the active substance is small, the active substance may be incorporated in a water soluble or water absorbing material and granulated with from five to fifty per cent of a water-insoluble binding material, either dissolved in an organic solvent or in a molten state. The water soluble or water absorbing material may be a carbo-hydrate, for example lactose, sucrose, dextrin or a cellulose derivative; a protein, for example, gelatin or casein; a water soluble wax, for example a polyethylene glycol; or an inorganic substance, for example kaolin or bentonite; a mixture of these or other suitable materials. The water-insoluble binding material may be a "plastic", for example polystyrene, polyvinyl acetate, polyvinyl chloride, polythene or a nylon derivative; or it may be a cellulose derivative, for example cellulose acetate or ethyl cellulose. The granules normally require a lubricating material, for example magnesium stearate, talc or graphite. If the medicated layer material is rather light, a heavy material, for example iron powder or titanium dioxide, may be incorporated in the granules to increase the density. When a mixture of inorganic oxides are required to liberate trace elements over a period of one or two years, the compressed product may be heated, so that the granules partially fuse together to form a hard metallic pellet.

Another method of coating the core is to use the conventional pan coating technique. The required number of cores are put into

a coating pan which is rotated, and the outer layer is formed by pouring or spraying on to the cores a solution or suspension of the active substance with suitable diluents and binding materials in a volatile material. For example, the active substance may be dissolved or suspended in a solution of a "plastic" in an organic solvent, such as cellulose acetate in acetone, which gives a tough water permeable medicated layer when applied to the cores. When the proportion of the active substance is small or when the active substance is relatively insoluble in water, a water soluble material, for example a polyethylene glycol, may be included to increase the permeability of the medicated layer to the required degree. Coating is continued, drying when necessary, until a medicated layer of the required weight has been obtained.

The coating of the core may also be achieved by dipping the core into a liquid preparation of the outer layer materials, or by moulding a preparation of the outer layer materials around the core.

The invention will now be described with reference to the following examples, in which all the temperatures are given in degrees Centigrade and the symool # designates the standard size of the mesh of the sieve used, as defined in the British Pharmacopoeia, 1958, page 968.

#### EXAMPLE 1

Core granules were prepared from:

Reduced iron 80 # - - - 500 g.  
The powder was granulated with 10% aqueous gelatin solution, sifted 20 # and dried at 50°, and 5.0 g. of magnesium stearate were mixed into the dried material.

Layer granules were prepared from:

Cobaltic oxide 80 # - - - 450 g.  
Kaolin 80 # - - - 50 g.  
The powders were mixed, granulated with water, sifted 30 # and dried at 50°, and 5.0 g. of magnesium stearate were mixed into the dried material.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 3.0 g., to produce a pellet with hemispherical ends. The pellets produced were heated to 1000° and held at that temperature for ten minutes.

#### EXAMPLE 2

Core granules were prepared from:

Reduced iron 80 # - - - 500 g.  
The powder was granulated with 10% aqueous gelatin solution, sifted 20 #, and dried at 50°, and 25 g. of graphite were mixed into the dried material.

Layer granules were prepared from:

Reduced iron 80 # - - - 400 g.  
Cobaltic oxide 80 # - - - 180 g.  
Cuprous oxide 80 # - - - 20 g.  
The powders were mixed, granulated with

10% aqueous gelatin solution, sifted 20 # and dried at 50°, and 30 g. of graphite were mixed into the dried material.

- 5 The granules were compressed on a compression coating machine with a core weight of 4.0 g. and a layer weight of 2.1 g., to produce a pellet with hemispherical ends. The pellets produced were heated up to 500° in a furnace and allowed to cool.

#### 10 EXAMPLE 3

Core granules were prepared from:

Reduced iron 80 # - - - 500 g.

Cupric oxide 80 # - - - 50 g.

- 15 The powders were mixed, granulated with 10% aqueous gelatin solution, sifted 20 # and dried at 50°, and 5.0 g. of magnesium stearate were mixed into the dried material.

Layer granules were prepared from:

Reduced iron 80 # - - - 305.1 g.

- 20 Cobaltic oxide 80 # - - - 88.2 g.

Manganese dioxide 80 # - - - 113.7 g.

Cuprous oxide 80 # - - - 88.2 g.

Zinc oxide 80 # - - - 6.3 g.

- 25 The powders were mixed, granulated with 10% aqueous gelatin solution, sifted 20 # and dried at 50°, and 3.0 g. of magnesium stearate were mixed into the dried material.

- 30 The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 2.2 g., to produce a pellet with hemispherical ends. The pellets were heated up to 500° in a furnace and allowed to cool.

#### 35 EXAMPLE 4

Core granules were prepared from:

Reduced iron 80 # - - - 500.0 g.

- 40 The powder was granulated with 5% acrylic resin in chloroform, sifted 20 # and dried at 50°, and 25 g. of graphite were mixed into the dried material.

Layer granules were prepared from:

Penicillin G. - - - - - 66.6 g.

(or =  $100 \times 10^6$  units)

- 45 Sucrose - - - - - 200.0 g.

Polystyrene - - - - - 50.0 g.

- 50 The Penicillin G. and sucrose were mixed and granulated with the polystyrene which was dissolved in 250 mls. of chloroform. The mixture was dried and sifted 20 #. 3.0 g. of magnesium stearate were mixed into the dried material.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 3.16 g.

#### 55 EXAMPLE 5

Core granules were prepared as in Example

3. Layer granules were prepared from:

- 60 Polymyxin B. sulphate - - - 200 g.

Lactose - - - - - 100 g.

Reduced iron - - - - - 100 g.

Polystyrene - - - - - 50 g.

The powders were mixed, granulated with the polystyrene which was dissolved in 200 mls. chloroform, sifted 20 # and dried. 4.0 g. of magnesium stearate were mixed into the dried material.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 4.5 g.

#### EXAMPLE 6

Core granules were prepared as in Example

2. Layer granules were prepared from:

Stilboestrol - - - - - 30 g.

Polyethylene glycol 4000 - - - 200 g.

Polyvinyl acetate - - - - - 100 g.

The polyethylene glycol 4000 was melted and the polyvinyl acetate dissolved in it. The stilboestrol was mixed in and the liquid cooled until hard. The mass was broken up and sifted 20 #, and 3.0 g. of magnesium stearate were added.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 2.2 g.

#### EXAMPLE 7

Core granules were prepared as in Example

3. Layer granules were prepared from:

Hexoestrol - - - - - 60 g.

Polyethylene glycol 4000 - - - 100 g.

Titanium dioxide - - - - - 100 g.

Polyvinyl acetate - - - - - 75 g.

The polyethylene glycol 4000 was melted and the polyvinyl acetate dissolved in it. The hexoestrol and titanium dioxide were mixed in and the mass cooled until hard. The mass was broken up and sifted 20 #, and 3.0 g. of magnesium stearate were added.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 2.3 g.

#### EXAMPLE 8

Core granules were prepared as in Example

2. Layer granules were prepared from:

Mepyramine maleate - - - 50 g.

Lactose - - - - - 100 g.

Kaolin - - - - - 100 g.

Polythene - - - - - 50 g.

The powders were mixed and granulated with the polythene which was dissolved in hot toluene. The mass was sifted 20 # and dried at 50°, and 3.0 g. of magnesium stearate were mixed into the dried material.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 3.0 g.

#### EXAMPLE 9

Core granules were prepared as in Example

3. Layer granules were prepared from:

Chlorocyclizine hydrochloride - 100 g.

Lactose - - - - - 100 g.

Reduced iron - - - - - 100 g.

Polythene - - - - - 50 g.

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The powders were mixed and granulated with the polythene which was dissolved in hot xylene. The mass was cooled, sifted 20 # and dried at 50°, and 3.5 g. of magnesium stearate were added and mixed into the dried material.

The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 3.5 g.

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## EXAMPLE 10

Core granules were prepared as in Example

3.

Layer granules were prepared from:

- 15    Triprolidine hydrochloride - 7.5 g.  
      Hydrogenated castor oil - 140.0 g.  
      Magnesium stearate - 100.0 g.  
      Edible bone phosphate - 60.0 g.

20    The hydrogenated castor oil was melted and the magnesium stearate, bone phosphate and triprolidine hydrochloride added. The mixture was stirred until hard. The cold mass was broken up and sifted 30 #.

25    The granules were compressed on a compression coating machine, with a core weight of 4.0 g. and a layer weight of 3.075 g.

## EXAMPLE 11

30    Reduced iron was granulated with 10% aqueous gelatin solution sifted 20# and dried at 50°. The granules were compressed 5.0 g. products, with hemispherical ends. The cores so formed were put into a tablet-coating pan and were coated with a 10% solution of cellulose acetate in acetone containing 1% Brilliant Green, drying after each coat until each  
 35    pellet contained 0.3 g. of the Brilliant Green. The pellets were dried at 50°.

## EXAMPLE 12

40    Reduced iron with 10% cuprous oxide was granulated with 10% aqueous gelatin solution, sifted 20 # and dried. The granules were compressed into 5.0 g. products, with hemispherical ends. The cores so formed were coated by dipping into a solution of 20%  
 45    ethylcellulose, 2% polyethylene glycol and 4% procaine penicillin in ethyl alcohol. The products were dipped and dried until a layer weight of 3.0 g. was obtained.

## WHAT WE CLAIM IS:—

50    1. A pellet for administration to a ruminant to supply it with a biologically active substance for an extended period of time, said pellet having a density and weight which relatively permanently retains it in the rumeno-reticular sac of the animal after administration and lodgement in the sac and embodying a core of density at least 3.5  
 55    around which there is an outer layer containing the biologically active substance which is released from the pellet into the contents of the sac over the extended period of time.  
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2. A pellet as claimed in claim 1 wherein the high density core contains iron.

3. A pellet as claimed in claims 1 or 2 wherein the biologically active substance is a hormone. 65

4. A pellet as claimed in claims 1 or 2 wherein the biologically active substance is an antibiotic.

5. A pellet as claimed in claims 1 or 2 wherein the biologically active substance is a trace element. 70

6. A pellet as claimed in claims 1 or 2 wherein the biologically active substance is an antihistamine. 75

7. A method for the manufacture of a pellet for administration to a ruminant to supply it with a biologically active substance for an extended period of time, said pellet having a density and weight which relatively permanently retains it in the rumeno-reticular sac of the animal after administration and lodgement in the sac and embodying the biologically active substance which is released from the pellet into the contents of the sac over the extended period of time, characterised in that a core of density at least 3.5 has applied around it an outer layer containing the biologically active substance. 80 85

8. A method as claimed in claim 7 wherein the outer layer is applied around the high density core by the compression coating technique. 90

9. A method as claimed in claim 7 wherein the outer layer is applied around the high density core by the pan coating technique. 95

10. A method as claimed in claim 7 wherein the outer layer is applied around the high density core by dipping the core in a liquid preparation of the outer layer. 100

11. A method as claimed in claim 7 wherein the outer layer is applied around the high density core by moulding a preparation of the outer layer around the core.

12. A method for the manufacture of a pellet for administration to a ruminant to supply it with a biologically active substance for an extended period of time, said pellet having a density and weight which relatively permanently retains it in the rumeno-reticular sac of the animal after administration and lodgement in the sac and embodying a core of density at least 3.5 around where there is an outer layer containing the biologically active substance which is released from the pellet into the contents of the sac over the extended period of time, substantially as herein described with reference to any one of the foregoing examples or any obvious equivalent thereof. 110 115 120

13. A pellet for administration to a ruminant to supply it with a biologically active substance for an extended period of time, said pellet having a density and weight which relatively permanently retains it in the rumeno-reticular sac of the animal after ad- 125

ministration and lodgement in the sac and  
embodying a core of density at least 3.5  
around which there is an an outer layer con-  
taining the biologically active substance which  
5 is released from the pellet into the contents

of the sac over the extended period of time  
substantially as herein described or ascer-  
tained or any obvious equivalent thereof.

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